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CLINICAL RESEARCH STUDY

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Association Between Alcohol Consumption and Both Osteoporotic Fracture and Bone Density

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ABSTRACT

OBJECTIVE: Alcoholism is a risk factor for osteoporotic fractures and low bone density, but the effects of moderate alcohol consumption on bone are unknown. We performed a systematic review and meta-analysis to assess the associations between alcohol consumption and osteoporotic fractures, bone density and bone density loss over time, bone response to estrogen replacement, and bone remodeling.

METHODS: MEDLINE, Current Contents, PsychINFO, and Cochrane Libraries were searched for studies published before May 14, 2007. We assessed quality using the internal validity criteria of the US Preventive Services Task Force.

RESULTS: We pooled effect sizes for 2 specific outcomes (hip fracture and bone density) and synthesized data qualitatively for 4 outcomes (non-hip fracture, bone density loss over time, bone response to estrogen replacement, and bone remodeling). Compared with abstainers, persons consuming from more than 0.5 to 1.0 drinks per day had lower hip fracture risk (relative risk = 0.80 [95% confidence interval, 0.71-0.91]), and persons consuming more than 2 drinks per day had higher risk (relative risk = 1.39 [95% confidence interval, 1.08-1.79]). A linear relationship existed between femoral neck bone density and alcohol consumption. Because studies often combined moderate and heavier drinkers in a single category, we could not assess relative associations between alcohol consumption and bone density in moderate compared with heavy drinkers.

CONCLUSION: Compared with abstainers and heavier drinkers, persons who consume 0.5 to 1.0 drink per day have a lower risk of hip fracture. Although available evidence suggests a favorable effect of alcohol consumption on bone density, a precise range of beneficial alcohol consumption cannot be determined.

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KEYWORDS: Alcohol; Bone mineral density; Hip fracture; Meta-analysis; Osteoporosis

The prevalence of low bone density among men and women aged more than 50 years has been estimated at greater than 44 million.[1] In this population, 1 in 2 women and 1 in 4 men develop osteoporotic fractures.[2] In addition to unmodifiable risk factors such as age and sex, bone density is influenced by modifiable lifestyle factors, including alcohol consumption.

Chronic heavy alcohol consumption is widely considered a risk factor for osteoporotic fractures and low bone density.[2] However, this relationship is based on small studies of men[3-7] and has not been established in women.[8] In contrast, several studies have reported that moderate alcohol use may decrease fracture rates and increase bone density.[9-18] In 2001, a National Institutes of Health panel concluded that "alcoholism" is a cause of osteoporosis but that "consumption of alcoholic beverages" has an inconsistent effect on bone.[19]

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We performed a systematic review and meta-analysis to assess the associations between alcohol consumption and osteoporotic hip and non-hip fractures, bone density and bone density loss over time, bone response to estrogen replacement, and bone remodeling. Our secondary aim was to examine whether the effect of alcohol on these outcomes is modified by sex.

CLINICAL SIGNIFICANCE

- Compared with abstinence, consuming 1 drink or less per day is associated with a lower risk of hip fracture, whereas consuming more than 2 drinks per day is associated with higher hip fracture risk.
- Greater alcohol consumption (up to 2 drinks per day) is linearly associated with higher bone density.
- Available literature is insufficient to determine the precise range of alcohol consumption that would maximize bone density and minimize hip fracture risk.

MATERIALS AND METHODS

Search Strategies

On May 14, 2007, we searched all Ovid MEDLINE databases, the Cochrane Central Register of Controlled Trials, Current Contents Connect, and PsychINFO. We defined search terms for alcohol consumption and each outcome (Appendix), and limited the results to human subjects and English language. We then manually searched references of included studies and pertinent reviews.

Study Selection

Two reviewers independently assessed each citation using predefined criteria. Included studies had experimental, cohort, or case-control designs; included adults both exposed and not exposed to alcohol; and reported on at least 1 outcome. We excluded studies in which alcohol consumption and bone density were measured once at the same point in time to avoid invalid assumptions about temporal sequence. To examine osteoporotic fracture rate, we identified studies of low-impact fractures of the hip, wrist, forearm, or vertebra. To evaluate bone density, we sought prospective studies in which bone density was assessed by central dual energy x-ray absorptiometry and measured after alcohol exposure. Studies examining bone density loss over time required bone density measures at 2 points in time. To examine the outcome of bone response to estrogen, we identified studies reporting the effect of alcohol on osteoporotic fracture rates or bone density among postmenopausal women taking estrogen replacement therapy. For the final outcome, bone remodeling, we included studies examining markers of bone formation and resorption (Appendix). Abstract ratings between reviewers had 92% agreement ($\kappa = 0.73$). Disagreements were resolved by discussion.

Assessment of Study Quality

We assessed study quality using the internal validity criteria of the US Preventive Services Task Force,[20] assigning a rating of "good" when all criteria were met, "fair" when 1 or more criterion was partially met and the study contained no fatal flaws, and "poor" if 1 or more criterion was not met and a fatal flaw invalidated the results. Studies of poor quality were excluded.

For our systematic review, studies were rated "good" if alcohol consumption was reported as a rate (eg, "drinks per day") and reflected data from more than a single survey item (ie, from separate questions about consumption of beer, wine, or spirits). Studies that used a single survey item, or did not sufficiently explain their measures, were rated "fair." Studies that used imprecise definitions of alcohol consumption (eg, "ever," "daily," or "yes") were rated "poor." In addition, we rated studies on the timing of their measurement of alcohol consumption. Prospective studies were rated "good" if alcohol consumption was measured at multiple time points and "fair" if alcohol consumption was measured at baseline only.

Prospective studies were rated "good" if fractures were ascertained by more than 1 source of information (eg, self-report verified by hospital records or a sample of specific *International Classification of Diseases* codes validated by chart review) and "fair" if only 1 information source was used. Case-control studies were rated "good" if cases were established using hospital records and "fair" if they were established by other means.

For all studies, we developed a predefined set of potential confounders that included age, body mass index, smoking, dietary calcium, physical activity, and estrogen exposure. "Good" studies adjusted for all potential confounders, "fair" studies adjusted for some confounders, and "poor" studies adjusted for age only. Differences were discussed until agreement was reached. Quality ratings between reviewers had 85% agreement ($\kappa = 0.67$).

Data Extraction

The first author (KMB) and 1 other author met to extract quantitative data on the association between alcohol consumption and the outcome, and adjustment for potential confounders. For example, data extracted may include the odds of hip fracture among those who consumed more than 0.4 drinks per day compared with abstainers (odds ratio = 0.69; 95% confidence interval [CI], 0.53-0.90), after adjusting for age, body mass index, smoking, and estrogen therapy.[21] One investigator was contacted by the first author to request numeric data that corresponded to a figure in the original study.[22] Because studies reported alcohol consumption using numerous units of measurement, we converted alcohol consumption into drinks per day by estimating that each standard drink is equivalent to 14 g or 0.6 fluid oz of

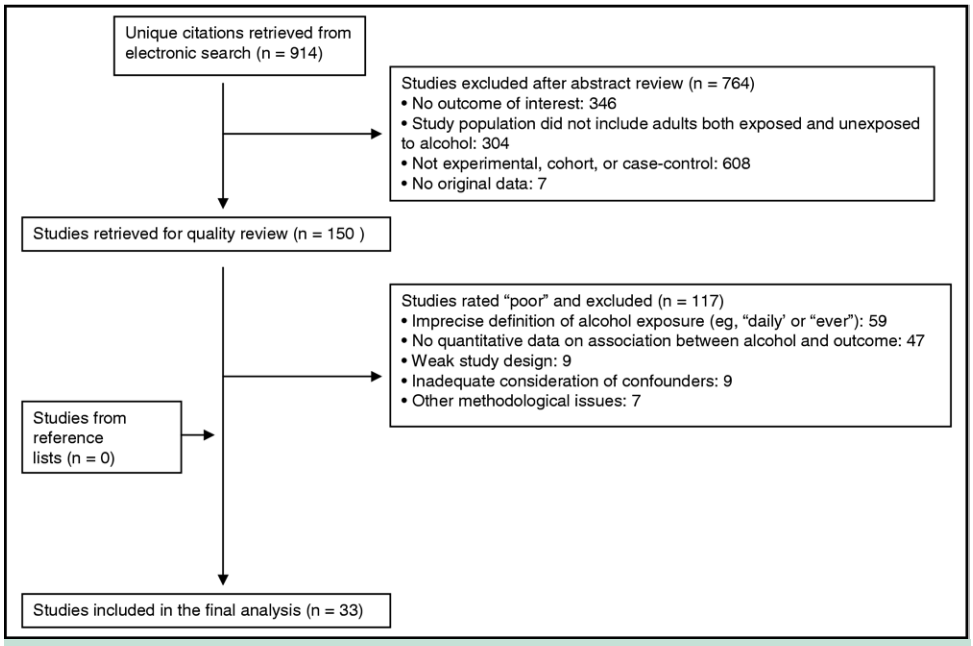

Figure 1 Study selection process. Studies may be excluded for multiple reasons.

pure alcohol,[23] that there are 29 kJ/g of alcohol,[24] and that 1 unit of alcohol equals 8 g of pure alcohol.[25]

Data Synthesis

For pooled estimates of the effect of alcohol consumption on hip fracture incidence, we extracted relative risk (RR) data, created strata of alcohol use, and performed a dose-response analysis using mean drinks per day when studies reported ranges of alcohol consumption. For the few studies that reported multiple categories of alcohol consumption within 1 defined strata, we "pooled first" using inverse variance weights. Given the rarity of events, RRs and odds ratios for hip fractures were considered equivalent. We combined fracture data by log transforming reported effects in each stratum and then pooled data with the random effects models.[26] Sex-stratification of the analysis of alcohol consumption and hip fracture was not possible because only 1 study reported results by sex.

For bone density, we pooled data using a dose-response regression model with adjustment for clustering within studies using inverse variance as analytic weights.[27] When necessary, we imputed variance using the method of Follman et al.[28] For each outcome, when no upper limit was given for the highest category of alcohol consumption, we multiplied the reported limit by 1.5, a method used in a similar meta-analysis.[29] We were unable to perform a meta-analysis of bone density loss over time because of the disparate outcomes reported (eg, beta-coefficient for the effect of alcohol on bone density loss, annual rate of bone density loss, or percentage of bone density loss). The results were not significantly different for men and women for any outcome except bone density loss over time.

Heterogeneity was assessed using the Q and I^2 statistics. Publication bias was assessed using the method of Egger et al.[30] All meta-analyses were performed using STATA (STATA 9.2, College Station, Tex).

RESULTS

Overview of the Evidence Base

The results of our search strategy are illustrated in Figure 1. Most studies were conducted in white, European, or American adults aged more than 50 years. The results were commonly adjusted for age, body mass index, and smoking. However, few studies adjusted for dietary calcium, physical activity, or estrogen exposure.

Alcohol Consumption and Hip Fracture Risk

Eight of 13 studies that examined the association between alcohol consumption and risk of hip fracture were prospective cohort studies,[33-40] and 5 were case-control studies[21,31,32,41,42] (Table 1). The case-control studies compared hospitalized cases with community controls,[21,32,41] hospitalized controls,[42] or both.[31] Cases and controls were matched on age, sex, race or ethnicity, and residential area,[31,32] or geographic location only.[21,41,42]

Meta-analysis of the effect of alcohol consumption on hip fracture risk revealed a J-shaped relationship, which is illustrated in Figure 2. Compared with abstainers, we found a lower risk of hip fracture among persons consuming up to 0.5 drinks per day (RR = 0.84 [95% CI, 0.70-1.01] Q = 091, $I^2 = 0.00$, publication bias $P = .39$) and persons consuming from more than 0.5 to 1 drink per day (RR = 0.80 [95% CI, 0.71-0.91] Q = 12.66, $I^2 = 0.21$, publication bias $P = .43$). Those consuming from more than 1 to 2 drinks per day did

not differ from abstainers (RR = 0.91 [95% CI, 0.76-1.09] Q = 11.33, $I^2 = 0.24$, publication bias $P = .72$), and persons consuming more than 2 drinks per day had a higher risk of hip fracture (RR = 1.39 [95% CI, 1.08-1.79] Q = 6.73, $I^2 = 0.24$, publication bias $P = .38$).

Alcohol Consumption and Fracture of the Forearm, Wrist, or Vertebrae

Of the 3 cohort studies that examined the effect of alcohol consumption on fracture of the forearm or wrist, 2 found no significant association[40,43] and 1 found that women consuming 1.8 drinks or more per day had a higher risk of wrist fracture compared with abstainers (RR 1.38 [95% CI, 1.09-1.74]).[39] Two studies examined the relationship between alcohol consumption and risk of vertebral fracture; 1 found no significant association,[40] and 1 found increased odds of fracture among men who consumed more than 0.3 drinks per day compared with abstainers (adjusted odds ratio 4.61 [1.19-17.90]).[44]

Alcohol Consumption and Bone Density

Four cohort studies assessed the association between alcohol consumption and bone density (Table 2).[12,13,16,33] Overall, there was a linear relationship between femoral neck bone density and alcohol consumption (Figure 3). Each drink per day was associated with an increase in femoral neck bone density of 0.045g/cm^2 (95% CI, 0.008-0.082 g/cm^2, $P = .01$). A significant linear relationship also was found at the vertebral spine (data not shown).

Alcohol Consumption and Bone Density Loss Over Time

Four prospective cohort studies[22,46-48] and 1 nested case-control study[45] examined the association between alcohol consumption and bone density loss over time (Table 3).[44-48] Two of the 3 studies that reported sex-stratified results found that the pattern of association between alcohol consumption and bone density loss was different in men and women.[46,47]

Bone Density Loss Over Time in Women. Four of the 5 studies that examined alcohol consumption and bone density loss over time in women found that women with greater alcohol consumption had lower bone density loss.[21,45-48] Of the 5 studies, 2 studies measured alcohol consumption continuously and found a significant inverse linear association between alcohol consumption and bone density loss.[45,46] Two other studies measured alcohol consumption categorically and found the lowest bone density loss among women with the greatest alcohol consumption (approximately 1-2 drinks per day).[22,47] The final study found a U-shaped relationship between alcohol consumption and bone density loss, with the lowest bone density loss among women consuming 0.2 to 1.7 drinks per day and higher bone density loss among both abstainers and women consuming more than 1.7 drinks per day.[48]

Bone Density Loss Over Time in Men. Of the 3 studies that assessed alcohol consumption and bone density loss over time in men, 2 reported U-shaped relationships.[47,48] The lowest bone density loss was among men in the middle drinking categories (between 0.7 and either 1.4 or 1.7 drinks per day), and higher bone density loss was among men with either little or no alcohol consumption and men with the greatest alcohol consumption (at least 1.4 or 1.7 drinks per day). The third study found no linear relationship between continuous alcohol consumption and bone density loss in men.[46]

Alcohol Consumption and Bone Response to Estrogen Replacement

Two studies assessed the effect of alcohol consumption on bone response to estrogen therapy. One prospective cohort study found that estrogen therapy was independently associated with a 74% lower risk of hip fracture (RR 0.36 [95% CI, 0.14-0.90]) among women who consumed 1 drink or more per day, compared with abstainers.[49] The other was a nested case-control study that defined cases ("good" responders) as women who gained more bone density during 5 years of follow-up than the upper 95th percentile of an untreated group.[45] After adjustment for multiple potential confounders, alcohol intake was independently associated with being a "good" responder to estrogen therapy.

Alcohol Consumption and Markers of Bone Remodeling

Markers of Bone Formation. Osteocalcin, a vitamin K-dependent protein synthesized by osteoblasts, is widely used as a clinical marker of bone formation. In 6 experimental studies of heavy drinkers (7-16 drinks per day), the subjects served as their own controls. Osteocalcin levels were measured before and after periods of abstinence ranging from 7 days to 2 years.[8,50-54] All studies found that osteocalcin increased significantly after abstinence.

Two additional experimental studies found consistent results after administering alcohol to healthy male adults.[55,56] The doses of alcohol varied from 1.8 drinks given over 45 minutes[55] to 4 drinks administered daily for 3 weeks.[56] Both studies found a significant decrease in osteocalcin levels during alcohol administration.

Three of the abstinence studies also examined changes in carboxy-terminal propeptide of type I procollagen,[8,52,54] a protein representing synthesis of type-1 collagen. All found a significant increase in carboxy-terminal propeptide of type I procollagen during abstinence.

Markers of Bone Resorption. Hydroxyproline, a modified amino acid that is released during the breakdown of collagen, was measured in 3 studies of heavy drinkers. During abstinence from alcohol, 1 study found a significant increase in urinary hydroxyproline,[54] and 2 studies found no significant change.[8,53]

Table 1 Studies of the Association between Alcohol Consumption and Risk of Hip Fracture

Study, year	Study Design	Sample Characteristics	Study Quality	Duration of Follow-up
Felson, 1988 (34)	Framingham Study cohort	5209 adults, aged 31–95 yrs	fair*	117,224 person-years
Hoidrup (men), 1999 (35)	Combined data from three cohort studies	17,868 men, aged 20–93 yrs	fair*	434,324 person-years
Hoidrup (women), 1999 (35)	Combined data from three cohort studies	13,917 women, aged 20–93 yrs	fair*	434,324 person-years
Kanis, 2004 (36)	Combined data from three cohort studies	16,971 adults, aged 25–103 yrs	fair*†‡	75,433 person-years
Holbrook, 1988 (37)	Rancho Bernando cohort	957 adults, aged 50–79 yrs	fair*†‡	14 years
Hemenway, 1994 AmJPubHealth (38)	Health Professionals Follow-Up Study cohort	49,895 men, aged 40–75 yrs	fair*†‡	270,000 person-years
Hernandez-Avila, 1991 (39)	Nurses Health Study cohort	84,484 women, aged 29–74 yrs	fair*†	482,347 person-years
Hansen, 2000 (40)	Iowa Women's Health Study cohort	34,703 women, aged 55–69 yrs	fair†§	187,035 person-years
Mukamal, 2007 (33)	Cardiovascular Health Study cohort	5865 adults, aged ≥65 yrs	fair*	70,380 person-years
Cumming, 1994 (41)	Case-control	416 adults, aged 65–100 yrs (209 cases, 207 controls)	fair*	NA
Baron, 2001 (21)	Case-control	4589 postmenopausal women (1,327 cases, 3,262 controls)	fair*	NA
Grisso, 1994 (31)	Case-control	543 black women (144 cases, 399 controls)	fair*‡	NA
La Vecchia, 1991 (42)	Case-control	1658 women, aged 29–74 yrs (209 cases, 1449 controls)	fair*	NA
Suzuki, 1997 (32)	Case-control	747 adults, aged 65–89 yrs (249 cases, 498 controls)	fair*‡	NA

*Incomplete adjustment for potential confounders (age, body mass index, smoking, dietary calcium, physical activity, and estrogen exposure in women).

†alcohol consumption measured at baseline only (prospective studies).

‡1 survey item to measure alcohol consumption or poor explanation of measurement methods

§fractures ascertained from a single source (prospective studies); II cases not established using hospital records (case-control studies); NA indicates not applicable; BMI indicates body mass index; CVA indicates cerebrovascular accident; DM indicates diabetes mellitus; "Former drinkers" defined as participants who reported abstinence at baseline but at a follow-up visit responded "yes" to either a "change in pattern of drinking in the past 5 years" or "ever regularly consumed ≥ drinks daily".

¶Gaps in categories due to conversion from drinks per week to drinks per day.

Table 1 Continued

Timing of Measurement of Alcohol Use	Events	Potential Confounders Adjusted for in Analysis	Unit of Analysis of Alcohol	Magnitude of Association (95% CI)
Baseline and years 4, 10, 20, 22, 24, 26, and 30	217	Age, sex, weight, smoking	per 7 oz/wk	Odds Ratio: 1.28 (1.05–1.56)
Baseline and between 1 and 3 follow up interviews	307	Age, BMI, smoking, physical activity, original cohort, education, cohort of origin	<0.1 drinks/day 0.1–0.9 drinks/day 1–1.9 drinks/day 2–3.9 drinks/day 4–5.9 drinks/day 6–9.9 drinks/day >10 drinks/day	Relative Risk: 1.00 0.89 (0.58-1.38) 0.84 (0.54-1.30) 0.84 (0.54-1.32) 1.74 (1.06-2.89) 1.84 (1.00-3.41) 5.28 (2.60-10.70)
Baseline and between 1 and 3 follow up interviews	500	Age, BMI, smoking, physical activity, original cohort, education, cohort of origin	<0.1 drinks/day 0.1–0.9 drinks/day 1–1.9 drinks/day 2–3.9 drinks/day >4 drinks/day	Relative Risk: 1.00 0.89 (0.71–1.12) 1.01 (0.77–1.33) 1.32 (0.92–1.87) 1.01 (0.37–2.75)
Unspecified	279	BMD	0.6 drinks/day >1.1 drinks/day) >1.7 drinks/day >2.3 drinks/day	Relative Risk: 1.00 1.70 (1.20–2.42 2.05 (1.35–3.11) 2.39 (1.39–4.09)
Baseline	33	Age, sex, BMI, smoking	per 0.9 drinks/day	Relative Risk: 1.00
Baseline	67	Age, BMI, smoking, height	0 drinks/day 0–1.1 drinks/day 1.1–2.1 drinks/day >2.1 drinks/day	Relative Risk: 1.00 1.06 (0.58–1.93) 0.95 (0.42–2.17) 0.91 (0.38–2.17)
Baseline	65	Age, BMI, menopausal status, estrogen therapy, calcium use, caffeine exposure	0 drinks/day 0–0.4 drinks/day 0.4–1.1 drinks/day 1.1–1.8 drinks/day ≥1.8 drinks/day	Relative Risk: 1.00 0.94 (0.35–2.68) 1.99 (0.97–4.07) 1.15 (0.51–2.61) 2.33 (1.18–4.57)
Baseline	275	Age, BMI, smoking, physical activity, estrogen therapy, calcium use, caffeine exposure, calories, waist:hip ratio	0 drinks/day <0.3 drinks/day ≥0.3 drinks/day	Relative Risk: 1.00 0.92 (0.68–1.24) 0.79 (0.57–1.10)
Baseline and annually for 9 or 10 years	412	Age, sex, smoking, weight, height, leisure time physical activity, difficulty arising from a bed or chair, estrogen therapy, thiazide type diuretics, thyroid agents, race, diabetes, hypertension, cardiovascular disease, visual problems, arthritis, previous cancer, weight in early teens, Mini-Mental Status Exam score	0 drinks/day¶ former drinkers <0.14 drinks/day 0.14–0.86 drinks/day 1–1.86 drinks/day ≥2 drinks/day	Hazard Ratio 1.00 0.84 (0.50–1.43) 0.77 (0.61–0.98) 0.83 (0.61–1.12) 0.82 (0.53–1.26) 1.20 (0.74–1.95)
NA	NA	Age, sex	0 drinks/day <1 drinks/day ≥1 drinks/day	Odds Ratio: 1.00 0.70 (0.50–1.20) 0.60 (0.30–1.30)
NA	NA	Age, BMI, smoking, estrogen therapy	nondrinkers drinkers <0.2 drinks/day 0.2–0.4 drinks/day >0.4 drinks/day	Odds Ratio: 1.00 0.70 (0.60–0.82) 0.72 (0.59–0.88) 0.70 (0.56–0.87) 0.69 (0.53–0.90)
NA	NA	Age, BMI, area of residence	0–0.1 drinks/day 0.1–0.9 drinks/day ≥1 drinks/day	Odds Ratio: 1.00 1.3 (0.6–2.9) 2.2 (0.9–5.7)
NA	NA	Age, BMI, smoking, estrogen therapy, education, area of residence	0 drinks/day <2 drinks/day 2–3 drinks/day >3 drinks/day	Relative Risk: 1.00 0.7 (0.5–1.1) 1.2 (0.8–1.8) 1.0 (0.5–1.8)
NA	NA	BMI, physical activity, coffee and green tea, rural residence, main work activity, sleep disturbance, CVA hemiplegia, DM, milk, fish, sun exposure, immobilization, difficulty bathing independently, type of bed	0 drinks/day <1.9 drinks/day ≥1.9 drinks/day	Odds Ratio: 1.00 0.51 (0.29–0.89) 0.77 (0.33–1.79)

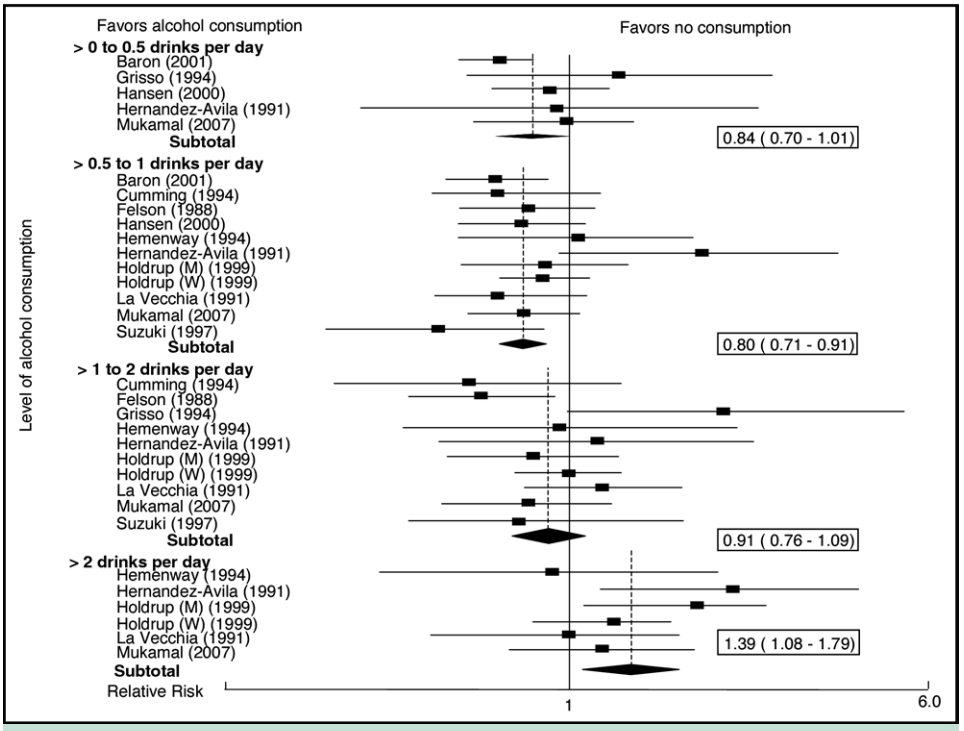

Figure 2 Association between alcohol consumption and hip fracture risk. Reference exposure is zero drinks per day. Size of data marker represents sample size. Horizontal lines denote 95% confidence intervals.

Table 2 Studies of the Association between Alcohol Consumption and Bone Mineral Density

Study, Year	Sample Characteristics	Study Quality	Duration of Follow-up	Measurement of Alcohol Consumption	Outcome Measure
Mukamal, 2007 (33)	5865 adults, aged ≥ 65 yrs	fair*	12 years	Baseline and annually for 9 or 10 years	femoral neck BMD
Holbrook et al. (Rancho Bernando), 1993 (13)	267 women, mean age 60 yrs	fair*	12 yrs	Baseline and year 12	femoral neck BMD
Felson et al. (Framingham Study), 1995 (12)	1,154 adults, aged 68–96 yrs (data shown for women)	fair*	20 yrs	Baseline and years 2, 4, 6, 8, 10, 12, 14, and 16	femoral neck BMD
Feskanich et al. (Nurses' Health Study), 1999 (16)	188 women, aged 50–74	fair*	14 yrs	Baseline and years 4, 6, and 10	femoral neck BMD
Holbrook et al. (Rancho Bernando), 1993 (13)	182 men, mean age 59 yrs	fair*	12 yrs	Baseline and year 12	femoral neck BMD
Felson et al. (Framingham Study), 1995 (12)	1,154 adults, aged 68–96 yrs (data shown for men)	fair*	20 yrs	Baseline and years 2, 4, 6, 8, 10, 12, 14, and 16	femoral neck BMD

*Incomplete adjustment for potential confounders (age, body mass index, smoking, dietary calcium, physical activity, and estrogen exposure in women); NS indicates "not significant". BMD indicates bone mineral density; BMI indicates body mass index; "Former drinkers" defined as participants who reported abstinence at baseline but at a follow-up visit responded "yes" to either a "change in pattern of drinking in the past 5 years" or "ever regularly consumed ≥5 drinks daily".

†Gaps in categories due to conversion from drinks per week to drinks per day.

DISCUSSION

Our analysis demonstrates a J-shaped relationship between alcohol consumption and hip fracture risk, with persons consuming up to 1 drink per day having the lowest risk of hip fracture. In contrast, most data on alcohol consumption and bone density suggest a linear association between greater alcohol consumption and both higher bone density and lower bone density loss over time. Studies evaluating hip fracture risk included subjects with greater alcohol consumption than studies evaluating bone density, which may explain why the association between alcohol consumption and hip fracture was J-shaped rather than linear. Because studies of alcohol consumption and bone density included few heavier drinkers, current evidence is insufficient to determine a precise amount of alcohol consumption that is associated with higher bone density.

Compared with abstainers, moderate drinkers had lower hip fracture risk and heavier drinkers had higher hip fracture risk. However, important biases may have influenced these results. It is likely that falls contributed to the observed increase in hip fracture risk among heavier drinkers. Further, most categories of nondrinkers included both lifetime abstainers and former drinkers. If former drinkers stopped for health reasons, this may partially explain the higher hip fracture risk among nondrinkers.

In contrast with the J-shaped association between alcohol consumption and hip fracture risk, pooled data suggest a linear relationship between alcohol consumption and bone density. These data were derived from studies mainly of individuals consuming less than 2 drinks per day. Because these studies may have been underpowered to demonstrate changes in bone density at greater alcohol consumption levels, the observed linear association may not fully describe this relationship. In addition, the increase in bone density associated with each additional drink per day was small in magnitude and of uncertain clinical significance.

The exact mechanism by which alcohol influences bone density is not clear. Putative biological mechanisms for a beneficial effect of alcohol on bone density include increases in the concentration of serum estradiol[57,58] and liver estrogen receptors.[59] However, as has been suggested regarding other beneficial effects of moderate alcohol consumption, the observed benefit may reflect confounding by unmeasured healthy behaviors.[60,61] An important limitation of the existing literature, and the reason most studies were rated "fair," is that few studies sufficiently adjusted for major potential confounders, and none included markers of socioeconomic status. Although our finding that alcohol consumption augments the benefits of estrogen therapy is based on a small number of studies, it is consistent with research suggesting that alcohol ingestion leads to elevations in circulating estradiol levels in women taking

Table 2 Continued

Potential Confounders Adjusted for in Analysis	Statistical Measure of Association	Unit of Analysis of Alcohol	BMD (g/cm2)	*p* Value
Age, sex, smoking, weight, height, leisure time physical activity, difficulty arising from a bed or chair, estrogen therapy, thiazide type diuretics, thyroid agents, race, diabetes, hypertension, cardiovascular disease, visual problems, arthritis, previous cancer, weight in early teens, Mini-Mental Status Exam score	F-tests	0 drinks/day†	0.69	<0.001
		former drinkers	0.72	
		<0.14 drinks/day	0.69	
		0.14–0.86 drinks/day	0.70	
		1–1.86 drinks/day	0.73	
		≥ 2 drinks/day	0.74	
Age, smoking, BMI, exercise and estrogen therapy	χ^2	0 drinks/day	0.64	NS
		<0.5 drinks/day	0.63	
		0.5–1.2 drinks/day	0.62	
		>1.2 drinks/day	0.64	
Age, smoking, weight, height, age at menopause, durat ion of estrogen use	χ^2	<0.2 drinks/day†	0.71	NS
		0.2–0.4 drinks/day	0.70	
		0.7–1.4 drinks/day	0.71	
		≥1.7 drinks/day	0.74	
Age, smoking, BMI, estrogen therapy, age at menopause	χ^2	<0.3 drinks/day	0.65	NS
		0.3–0.8 drinks/day	0.67	
		>0.8 drinks/day	0.67	
Age, smoking, BMI, exercise	χ^2	0 drinks/day	0.68	<0.01 for trend
		<0.9 drinks/day	0.72	
		0.9–1.8 drinks/day	0.78	
		>1.8 drinks/day	0.75	
Age, smoking, weight, height	χ^2	<0.2 drinks/day	0.86	NS
		0.2–0.4 drinks/day	0.86	
		0.7–1.4 drinks/day	0.88	
		1.7–2.9 drinks/day	0.85	
		≥3 drinks/day	0.88	

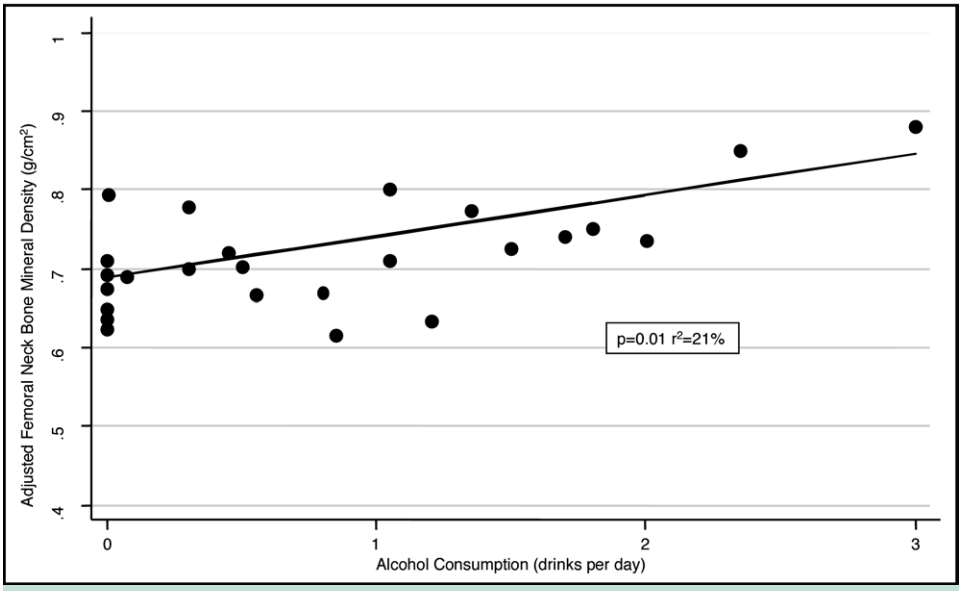

Figure 3 Association between alcohol consumption and adjusted femoral neck bone mineral density. Adjustment for confounders is variable. Study adjusting for the fewest covariates controlled for age, smoking, weight, and height. Study adjusting for the most covariates also controlled for leisure time physical activity, difficulty arising from a bed or chair, estrogen therapy, thiazide-type diuretics, thyroid agents, race, diabetes, hypertension, cardiovascular disease, visual problems, arthritis, previous cancer, weight in early teens, and Mini-Mental Status Exam score.

Table 3 Studies of the Association between Alcohol Consumption and Bone Mineral Density Loss Over Time

Study, Year	Sample Characteristics	Study Quality	Duration of Follow-up	Measurement of Alcohol Consumption	Outcome (Unit)
BMD loss at the femoral neck among women					
Dennison et al. 1999 (46)	143 women, aged 60–75 yrs	fair*‡	4 yrs	Baseline and year 4	Annual BMD loss at the femoral neck
Rejnmark et al. (Danish Osteoporosis Prevention Study), 2004 (45)	932 women, mean age 49 yrs	fair*†‡	5 yrs	Baseline	BMD loss at the femoral neck (g/cm2)
Macdonald et al. 2004 (22)	891 women, aged 45–55 yrs	fair*	5–7 yrs	Baseline and year 5	Annual BMD loss at the femoral neck (%/yr)
Burger et al. (Rotterdam Study), 1998 (47)	2452 women, mean age 67 yrs	fair*†‡	median 1.9 yrs	Baseline	Annual BMD loss at the femoral neck (g/cm2/yr)
Hannan et al. (Framingham Osteoporosis Study), 2000 (48)	486 women, aged 67–90 yrs	fair*†‡	4 yrs	Baseline	Percent BMD loss at the femoral neck (%)
BMD loss at the femoral neck among men					
Burger et al. (Rotterdam Study), 1998 (47)	1856 men, mean age 67 yrs	fair†‡	median 1.9 yrs	Baseline	Annual BMD loss at the femoral neck (g/cm2/yr)
Hannan et al. (Framingham Osteoporosis Study), 2000 (48)	278 men, aged 67–90 yrs	fair*†‡	4 yrs	Baseline	Percent BMD loss at the femoral neck (%)
Dennison et al. 1999 (46)	173 men, aged 60–75 yrs	fair‡	4 yrs	Baseline and year 4	BMD loss at the femoral neck (%/yr)

*Incomplete adjustment for potential confounders (age, body mass index, smoking, dietary calcium, physical activity, and estrogen exposure in women).
†alcohol consumption measured at baseline only.
‡1 survey item to measure alcohol consumption or poor explanation of measurement methods. BMD indicated bone mineral density; BMI indicates body mass index; NS indicates not significant; NR indicates not reported.

estrogen replacement therapy.[62-64] Because of this association, studies that did not control for estrogen exposure may be particularly vulnerable to bias.

Most studies of bone density loss in women demonstrated an inverse linear relationship between alcohol consumption and bone density loss over time, whereas most studies in men reported a J-shaped relationship. Although sex differences in the effect of alcohol consumption on bone density have been suggested,[65] observed differences might be explained by differences in alcohol exposure. Studies of bone density loss over time frequently combined moderate and heavy drinkers in a single category, making the greatest drinking category heterogeneous. For example, if the population of women categorized as consuming more than 1.4 drinks per day consumed less alcohol than men in the same drinking category, data from men and women would suggest different patterns of association between alcohol consumption and bone density due partly to misclassification. Further research is needed to characterize sex differences in the effect of alcohol on bone density loss over time.

Data from experimental studies indicate that osteocalcin increases after abstinence and decreases after alcohol administration. These results suggest a reversible suppression of bone formation when administered rapidly or in large doses, and are consistent with prior research.[66,67] The effect of long-term alcohol consumption on bone remodeling likely involves a complex uncoupling of formation and resorption.[68] Heavy alcohol consumption may have a direct acute negative effect on osteoblasts, but positive effects of alcohol on bone density may be due to indirect long-term hormonal effects.[69] The precise effects of moderate alcohol consumption on bone metabolism are still unknown.

A key limitation of many original studies in this review was the method and timing of alcohol consumption measurement, a weakness that has been noted by other reviews and meta-analyses of alcohol consumption.[29,70,71] Studies that measured alcohol consumption only at baseline are vulnerable to misclassification if exposure to alcohol changed before the outcome was measured. In addition, collecting data on alcohol consumption by self-report using simple surveys may lead to underreporting, particularly among heavy drinkers.[72,73] Despite this potential reporting bias, the rank order of alcohol consumption reported by individual studies is unlikely to be affected.

Because most included studies were observational, these results must be interpreted with caution. Although many benefits, including decreased mortality,[74] have been attributed to moderate alcohol consumption, the appropriateness

Table 3 Continued

Potential Confounders Adjusted for in Analysis	Statistical Measure of Association	Unit of Analysis of Alcohol	BMD Loss	Magnitude of Association	*p* Value
Age, smoking, BMI, change in BMI, activity, calcium intake, osteoarthritis grade	Beta-coefficient	per 0.1 drinks/day	NA	(−0.07)	0.007
Age, smoking, weight, waist to hip ratio, time since menopause, est rogen therapy, total energy, calcium, vitamin D intake, metabolic markers of metabolism	Beta-coefficient	per gram of alcohol/day	NA	(−0.048)	p < 0.001
Age, smoking, height, weight, weight change, BMD, activity, activity change, menopausal status, estrogen therapy, socioeconomic status, consuming a weight-reducing diet, osteoarthritis	Beta-coefficient	per quartile (medians) 0 drinks/day 0.2 drinks/day 0.5 drinks/day 1.0 drinks/day	NA	(−0.0893)	0.002
Age, smoking, BMI, calcium and energy intake, lower limb disability	Beta-coefficient	0 drinks/d 0–<0.7 drinks/day 0.7–<1.4 drinks/day >=1.4 drinks/day	0.0056 0.0042 0.0051 0.0027	NR	NS
Age, smoking, weight, weight change, height, estrogen therapy	Least squares mean	0–<0.2 drinks/day 0.2–0.7 drinks/day >0.7–1.7 drinks/day >1.7 drinks/day	2.39 2.05 2.28 3.09	NR	NS
Age, smoking, BMI, calcium and energy intake, lower limb disability	Beta-coefficient	0 drinks/day 0–<0.7 drinks/day 0.7–<1.4 drinks/day >=1.4 drinks/day	0.0057 0.0025 0.0012 0.0048	NR	NS
Age, smoking, weight, weight change, height	Least squares mean	0–<0.2 drinks/day 0.2–0.7 drinks/day >0.7–1.7 drinks/day >1.7 drinks/day	2.68 2.66 2.57 3.27	NR	NS
Age, smoking, BMI, change in BMI, activity, calcium intake, osteoarthritis grade	Beta-coefficient	per 0 .1 drinks/day	NA	NR	NS

of using nondrinkers as a reference group has been questioned.[75,76] To expand our understanding of the effects of alcohol on bone density, rigorous prospective studies are needed that carefully measure potential confounders. Because bone density reflects the cumulative effects of numerous factors on bone metabolism over long periods of time, future studies should adjust for baseline bone density.

CONCLUSIONS

Current best evidence on the effect of alcohol on bone density suggests that compared with abstinence, consumption of up to 1 drink per day is associated with a decreased risk of osteoporotic hip fracture. Further, most evidence supports a beneficial effect of moderate alcohol consumption on bone density. However, evidence is insufficient to determine relative associations between alcohol consumption and bone density in moderate compared with heavy drinkers.

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APPENDIX

Medical Subject Headings and Text Words Used in Literature Search

Concept	MeSH Terms	Text Words
Alcohol Consumption	Alcohol-related disorders Alcoholism Alcoholic beverages Alcohol drinking	Alcohol, alcoholic, alcoholism, beer, wine, liquor
Bone Mineral Density	Osteoporosis Postmenopausal osteoporosis Bone density Metabolic bone diseases Pathologic bone demineralization	Osteoporosis, osteopenia, bone mineral density, BMD, bone resorption
Osteoporotic Fractures	Fractures Spontaneous fractures Hip fracture Spinal fractures Wrist injuries	Compression fracture, fragility fracture, atraumatic fracture
Metabolism	Bone resorption	Telopeptide, n-telopeptide, c-telopeptide, osteocalcin, bone-Gla protein, BGP, bone and alkaline phosphatase, deoxypyridinoline, hydroxyproline, tartrate-resistant acid phosphatase, TRACP, bone and sialoprotein, hydroxylysine

BMD, Bone mineral density; *BGP,* beta-glycerophosphatase; *TRACP,* tartrate-resistant acid phosphatase.

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